GOOD MANUFACTURING PRACTICE

or

‘GMP’

A BRIEF GUIDE

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1. INTRODUCTION

This guide has been written for staff of the National Blood Service. Although written primarily for laboratory staff carrying out blood processing and testing operations, it is equally relevant for other NBS staff as GMP covers all aspects of 'manufacture', including collection, transportation, processing, storage, quality control, and delivery of the finished product.

This guide is not a definitive document and is based on the current version of "Rules and Guidance for Pharmaceutical Manufacturers and Distributors" (i.e. the "Orange Guide"). Your Quality Department can provide up to date information on GMP and its interpretation.

GMP provides a model on which to base a documented quality system and describes the practical activities and the controls which must be in place in order to be able to produce products which comply with their specification and are safe for use. Another model that is used for designing quality systems is ISO 9000, which is more oriented towards the management aspects of quality. GMP and ISO 9000 are to some extent supplementary, which explains why there may be aspects of NBS quality systems, which are not part of GMP requirements.

2. THE NEED FOR GOOD MANUFACTURING PRACTICE

People prescribing or being prescribed a medicine have little chance of detecting if it is faulty or not. People who take a medicine trust the doctor who wrote the prescription and the pharmacist who dispensed it. The doctor and pharmacist in turn put their trust in the manufacturer who has a fundamental role in ensuring that the medicine is fit for its purpose and is safe to use. In the case of a blood product the hospital Blood Bank is the "pharmacist" and the NBS is the "manufacturer".

Product testing of medicines and blood products on its own cannot ensure quality. This is because a lot of testing is destructive; meaning only samples from a batch can be tested. Blood products are made in 'batches of one' (i.e. each blood donation) and it is not possible to test all units for all the things that could have gone wrong.

GMP tries to ensure that quality is built into the organisation and the processes involved in manufacturing. The activities involved in achieving quality cover much more that the manufacturing operations themselves. There must be clear written specifications for the materials, the packaging and the products themselves. There must be clear written instructions and procedures covering processing and testing, handling, storage, receipt and dispatch. Suitable premises, equipment and trained staff must be specified and made available.

3. GMP AND QUALITY MANAGEMENT

GMP is defined as:
"That part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation or product specification".

Quality Assurance is defined as:
"The sum total of the organised arrangements made with the object of ensuring that medicinal products are of the quality required for their intended use".

The formal definition of Quality is:
"The totality of features and characteristics of a product or service which bear on its ability to meet stated or implied needs".

The aim of GMP is to build quality into the product (and the service). The control of quality begins long before we collect any blood, in activities such as designing buildings, specifying equipment, defining procedures and so on.

Quality has therefore been achieved when those needs have been met by a product or service that has the required features or characteristics. A feature is something tangible such as the volume of a unit of red cells. A characteristic is something less tangible such as the shelf life of unit of red cells.

Quality Control is the process by which we measure actual quality performance, compare it with a standard and take action if there are any differences. This process of comparison takes place during the production stages and when the product is ready for delivery. At this point we can use the product specification to compare with, at earlier stages there may need to be intermediate specifications.

In the NBS we use product (e.g. the "Red Book") and service specifications (e.g. published Guidelines and Hospital Contracts) as the written interpretation of customer needs.

One of the basic principles of GMP, which is echoed in ISO 9000, is for the responsibility for Quality Control to be held by somebody independent from the people responsible for production. This does not mean that the testing facilities need to be managed independently, but that the acceptance of the results of the testing must be independent, as must the initiation of any actions necessary after examining the results.

4. GMP REQUIREMENTS

The current version of "Rules and Guidance for Pharmaceutical Manufacturers and Distributors" has nine chapters, which have the following titles:

1. Quality Management
2. Personnel
3. Premises and Equipment
4. Documentation
5. Production
6. Quality Control
7. Contract Manufacture and Analysis
8. Complaints and Product Recall
9. Self Inspection

There are also a number of Annexes, some of which are relevant to our activities, such as those dealing with computer systems validation and irradiation.

The key points from each of the chapters, which are particularly relevant to the NBS, are listed below.

Quality Management

- The manufacturer must produce products that are fit for their intended use and do not place patients at risk.
- Senior management is responsible for product quality and safety but the participation and commitment of staff is vital, as is the support of suppliers.
- There must be a comprehensive and effectively implemented Quality Assurance system, incorporating Good Manufacturing Practice and Quality Control.
- The system should be fully documented and its effectiveness monitored.
- All parts of the Quality Assurance system should be adequately resourced with competent personnel and proper premises, equipment and facilities.

Personnel

- A satisfactory system of Quality Assurance depends on people.
- There must be sufficient qualified personnel to carry out the necessary tasks.
- The responsibilities of individuals should be clearly understood and recorded.
- All personnel should be aware of the principles of GMP.
- All personnel should receive initial and continuing training, relevant to their needs.

Premises and Equipment

- Premises and equipment must be built and maintained to suit the operations being carried out.
- The layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance.
- Premises and manufacturing equipment should be cleaned according to detailed written procedures.
- The entry of unauthorised people should be prevented and production and storage areas should not be used as a ‘right of way’.
- Measuring, weighing, recording and control equipment should be calibrated regularly.
- Defective equipment should be removed if possible or labelled as defective if not.

Documentation

- Clearly written documentation prevents errors from spoken communication.
- Specifications, instructions, procedures and records must be free from errors and available in writing.
- Documents should be unambiguous, have clear and concise contents, a title and purpose.
- Documents should be regularly reviewed and kept up to date.
- Documents should not be hand-written (except for the entry of data).
- Records should be completed in ink.

- Any alteration to a record should be signed and dated with the original entry still visible.

Production

- Production activities must follow clearly defined procedures and should be performed only by trained and competent people.
- All materials and products should be stored under the appropriate conditions and in an orderly fashion to permit batch segregation and stock rotation.
- At each stage of processing, products and materials should be protected from microbial and other contamination.
- Any deviation from instructions or procedures should be avoided. However, changes may be approved in writing by a competent person, with the involvement of the Quality Department if possible.
- Significant amendments to the manufacturing process, including any change in equipment or materials which may affect product quality and/or reproducibility of the process should be validated.
- Validation studies should be conducted to demonstrate that the process, equipment and/or activity actually leads to the expected results.

Quality Control

- Quality Control is not confined to laboratory operations, but must be involved in all decisions that may concern the quality of the product.
- The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control.
- Sampling of product should take place in accordance with written procedures.
- Analytical methods should be validated.

Contract Manufacture and Analysis

Not applicable to the NBS.

Complaints and Product Recall

- All complaints and other information concerning potentially defective products must be reviewed carefully according to written procedures.
- The person responsible for Quality Control should normally be involved in the study of product defects.
- There should be written recall procedures that are regularly checked and updated where necessary.
- Recall operations should be capable of being initiated promptly and at any time.

Self Inspection (Internal Audit)

- Internal Audits should be conducted in order to monitor the implementation and compliance with GMP.
- Internal Audits should be conducted in an independent and detailed way by designated competent persons.

5. PRACTICAL CONSIDERATIONS

In addition to the key aspects of the requirements that GMP imposes on us (listed above), there are some practical aspects of GMP, which affect all staff working in relevant areas.

Documentation

Most people dislike paperwork. Computers are taking over some of the work but we still have lots of paper in use, which although a 'nuisance', helps to keep our products safe. Documentation is needed to allow us to:

- Define in advance what we are going to do.
- Check that we have done what we should have done.
- Keep records of information, results and actions taken.
- Investigate problems.

There are a number of different types of document in use. Manufacturing and other instructions are contained within Standard Operating Procedures (SOPs), which describe specific tasks in a stepwise fashion, instructing staff what to do and if necessary how to do it, although the how is mainly part of training and job skills.

Although often called 'operating' procedures, there are other SOPs which deal with more general aspects of procedure such as validation, corrective action, quality incidents, training and so on which are mostly used by managers and supervisors.

Specifications for products and how they are to be tested are contained in documents such as the 'Guidelines for the Blood Transfusion Service' (i.e. the "Red Book"). We use these specifications when we are developing our manufacturing methods and particularly when drawing up our quality standards and test methods.

Labelling

We use labels for internal identification purposes and also to inform users about our products and about the contents of the container to which the label is attached. Labels are of vital importance. An incorrect label could lead to a disaster. There are some rules regarding the use of labels:

- They should always be held securely and not left lying around.
- Always notify somebody if labels are seen to be coming detached or appear to be incorrect or are in the wrong place.
- Report any labels that are damaged or dirty.
- Never remove a label which has been incorrectly applied and never stick a new label over an old one of the same type, although planned ""over-sticking"" e.g. putting a blood group label onto a base label is allowed.

Cleanliness

One of the requirements of GMP is to prevent contamination of products. Dust, particles and dirt can contaminate products as can chemicals and micro-organisms.

Dirt harbours micro-organisms and that is why our workplaces must be really clean, not just look clean.

The air is one source of contamination as are insects such as flies. People are also a source, which is why there are hygiene rules that must be followed. Key aspects of these rules are to maintain a high standard of personal hygiene, wear protective clothing as directed, never eat drink or smoke in work areas, keep your work areas clean and tidy and be on the alert for possible sources of contamination.

Training

GMP ultimately depends on people. The individual skills and understanding of people about their work can be developed by training. It is also important for product safety that staff do not carry out tasks for which they have not been trained and which either they or their supervisors think they are not competent to carry out.

Training should be given on both the theory and practice of the work being undertaken in a particular area, as well as relevant 'on -the-job' (i.e. task-based) training. Records of this training must be available.

6. GMP AND THE INDIVIDUAL

GMP concerns all people who work in areas where it applies, whether they are managers, supervisors or staff. It also affects those 'indirectly' involved, in activities such as maintenance, cleaning, record keeping and in 'support' areas such as the quality and personnel departments, etc. Although people working in GMP areas can be carrying out quite different tasks using different skills there are some basic rules which can be generally applied.

Basic Rules of GMP

Here is a list of the basic rules, required by GMP:

1. Make sure you have the correct written instructions before starting a task.
2. Do not carry out a task for which you have not been trained or in which you do not feel competent.
3. Always follow instructions precisely. Do not cut corners. If in doubt, ask.
4. Check that the equipment and the materials that you are using are the correct ones, as stated in the procedure.
5. Check that the equipment you are using is clean.
6. Always be on your guard for labelling errors.
7. Keep everything clean and tidy (including yourself!).
8. Always be on the look out for mistakes, defects and unusual events. Report them immediately.
9. Make clear accurate records of what was done and the checks carried out.

Ultimately quality depends on people. Although processes get more automated there are still many activities which require the constant care and attention of staff.

APPENDIX 1: BACKGROUND TO GMP

The pharmaceutical industry in the UK is regulated by law to protect patients and to ensure quality and safety. The Medicines Act 1968 is the key piece of legislation. The Act is given effect through various 'Statutory Instruments', which can be introduced by the Secretary of State. The first 'Guide to Good Pharmaceutical Manufacturing Practice' appeared in 1971, following the 1968 Act. It had no statutory force and described "measures for control of quality during manufacture and assembly, with particular reference to those aspects that are associated with safety". The guide was written with the "conviction that the control of quality begins before any materials are purchased, continues thorough manufacture, assembly and distribution, and cannot be 'inspected into' a product at the end of its processing". It contained a number of Principles followed by guidance. The aspects covered were:

Buildings and Surrounding Areas
Equipment
Cleanliness and Hygiene
Production Procedures and Documentation
Quality Control
Records
Transportation
Verification of Procedures

Although the chapter headings of the current version of GMP (shown in section 4 of this guide) have changed, the basic contents have not altered very much. GMP has therefore stood the test of time and should be respected as a fundamentally sound set of rules and guidance.

APPENDIX 2: LICENSING AND MHRA INSPECTIONS

The National Blood Service (NBS) has a "Manufacturer's Specials Licence" granted by the Medicine & Healthcare Products Regulatory Authority (MHRA). It is a 'specials' licence because we do not need a Marketing Authorisation or Product Licence, and do not have to have a Qualified Person to release product to our customers. The licence is granted to the NBS (which lists all manufacturing sites). For each site, a person must be named as being responsible for Production, Testing and Quality Control. These two people have particular responsibilities in relation to compliance with GMP and therefore with the licence requirements.

The licence runs for five years and approximately every two years each Centre and associated Collection Teams are subject to the same sort of rigorous inspections as pharmaceutical manufacturers. The Inspector compares our practices with GMP and also against our own procedures. This is done by examining what is being done, by asking questions of staff and by examining records.

If we are not complying with GMP this is called a 'failure to comply with GMP'. These are categorised as being "Critical", "Major" or "Other". A 'Critical' deficiency means that patient safety is or could be compromised by what is being done or not done. A 'Major' deficiency is a serious non-compliance with GMP, and an 'Other' deficiency is something that is important enough to be mentioned and requires to be rectified.

The inspector provides a verbal report before completion of the inspection. A written report is provided later. The site being inspected must provide the Inspector with a plan of corrective action stating what will be done to correct each deficiency and by when. The inspection is not closed until the Inspector is satisfied with the corrective actions and renewal of the Licence may be withheld if appropriate actions are not implemented in the agreed time-scale.